Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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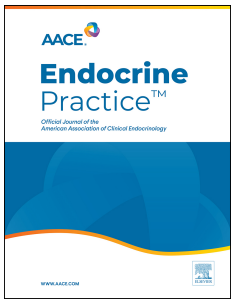

Euthyroid sick syndrome as a prognostic indicator of COVID-19 pulmonary involvement, associated with poorer disease prognosis and increased mortality

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Euthyroid sick syndrome as a prognostic indicator of COVID-19 pulmonary involvement, associated with poorer disease prognosis and increased mortality

Euthyroid sick syndrome in COVID-19

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Ethics Committee of Medical University of Lodz RNN/144/21/KE.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the

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Euthyroid sick syndrome as a prognostic indicator of COVID-19 pulmonary involvement, associated with poorer disease prognosis and increased mortality

Abstract

Objective

The prevalence of euthyroid sick syndrome (ESS) and its association with the prognosis of coronavirus disease 2019 (COVID-19) and mortality in patients with lung involvement by COVID-19 have not yet been elucidated.

Methods

Clinical and laboratory data of COVID-19 patients with or without ESS were collected retrospectively and analyzed on admission. All subjects were admitted to the Department of Internal Diseases and Clinical Pharmacology, Bieganski Hospital between December 2020 and April 2021.

Results

In total, 310 medical records from COVID-19 patients were analyzed retrospectively. Among 215 enrolled patients, 82 cases of ESS were diagnosed. The ESS patients had higher proinflammatory factor levels, longer hospitalization and a higher risk of requiring high flow nasal oxygen therapy or intubation than non-ESS patients. The Kaplan-Meier curve indicated that the patients with ESS had a lower probability for survival when computed tomography (CT) showed =< 50% parenchymal involvement, compared to those without ESS; however, no differences in mortality were noted in those with more than 50% parenchymal involvement . The survival curve showed that ESS was associated with a higher risk of mortality during hospitalization.

Conclusion

ESS is closely associated with poorer prognosis, including longer hospitalization, more frequent intubation and transfer to intensive care units (ICU) and a higher mortality rate in COVID-19 patients. ESS is a potential prognostic predictor of survival, regardless of lung involvement by COVID-19**.**

Keywords: Coronavirus Disease 2019 (COVID-19), euthyroid sick syndrome (ESS), disease severity

Introduction

In December 2019, the first case of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported in China. The virus went on to spread worldwide, resulting in the World Health Organization **(**WHO) declaring a pandemic in March 2020 [1]. As of 12 September 2021, 223 322 544 cases and 4 625 974 deaths had been reported globally [2] Observational studies suggest that the poor outcomes in COVID-19 patients may be partially explained by changes in thyroid hormone concentrations also seen in euthyroid sick syndrome (ESS) [3-6]. It is known that ESS is a condition that develops for many acute illness and can play an important role in predicting the outcome of critically-ill patients. In particular, free triiodothyronine (fT3) is believed to have considerable prognostic power regarding ICU mortality [7,8]. Furthermore, changes in thyroid hormone metabolism observed in muscle tissue during severe illness may explain the pathogenesis of respiratory failure [9-11].

ESS is characterized by alterations in thyroid function associated with acute illness. It is associated with a decrease in serum triiodothyronine (T3) level with no increase in thyroid stimulating hormone (TSH) level; this is believed to be associated with the suppression of peripheral thyroxine (T4) deiodination and reduced binding by plasma thyroid binding protein. Other potential abnormalities include decreased T4 level and increased serum reverse

triiodothyronine (rT3). A complete reversal of abnormalities in thyroid function tests is typically seen after recovery [12]. It remains unclear whether thyroid hormone replacement is beneficial for patients with ESS [13] so no patients with diagnosed ESS in our study received thyroid therapy.

Therefore, the aim of the present study was to assess whether patients hospitalized due to COVID-19 with ESS have a worse course of disease, increased need for oxygen therapy or greater % involvement of lungs, as revealed by computed tomography (CT) scans of the chest; it also examines whether they have a higher chance of intubation, ICU hospitalization and death. This is the first study to investigate the relationship between lung involvement, defined by the percentage extent of lesions visible on chest CT, and intensity of oxygen support in COVID-19 patents with or without ESS during hospitalization. It is also the first to propose a multivariate regression model for predicting mortality, intubation and high flow nasal oxygen therapy (HFNOT) in response to selected risk factors for severe COVID-19: the presence of ESS, and lung involvement (percentage of lung parenchyma involved with disease) indicated by chest CT. Our findings should be of value for clinicans working with COVID-19 patients with ESS.

Materials and Methods

Study design and participants

Data was collected retrospectively and included thyroid function tests from the medical records of 310 of adult COVID-19 patients (age >=18 years) hospitalized to the Department of Internal Diseases and Clinical Pharmacology, Bieganski Hospital in the period from December 2020 to April 2021. The patients were diagnosed with COVID-19 on admission, confirmed by the presence of SARS-CoV-2 RNA and antigens in nasal pharyngeal swab (NPS).

In total, 215 patients met the inclusion criteria which include hospitalization because of COVID 19 and thyroid function test done on admission to the hospital.

The following exclusion criteria were applied: preexisting hypothalamic-pituitary gland dysfunction in medical history; previous thyroid surgery; a history of chemotherapy or radiotherapy in the previous six months; alternation of the thyroid gland revealed by chest CT scan and described by radiologist, including nodular goiter; current use of thyroid hormone therapy; no full assessment of thyroid gland function examination on admission. Of the 95 patients who were excluded, the following reasons were given: lack of thyroid function test (n= 30), hypothyroidism (n=25), alternation of the thyroid gland revealed by chest CT scan and described by radiologist (n=10), hyperthyroidism (n=7) nodular goiter (n=9), radioiodine therapy (n=2), thyreoidectomy (n=6), multi-hormonal pituitary insufficiency (n=1), transfer from another unit (n=5).

To be qualified to the ESS group, a patient had to demonstrate decreased fT3 with normal or low TSH levels [14]. Patients with high TSH with normal free thyroxine (fT4) and fT3 were classified as having hypothyroidism, patients with low TSH and with normal fT4 and fT3 were classified as having hyperthyroidism and were excluded from the analysis.

Patient characteristics known to be associated with a higher risk for more severe COVID-19 (older age, sex, smoking and pre-existing medical conditions: malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke or transient ischemic attack) are presented in Table 1.

Data Collection

Patient age and sex were recorded on admission (between 0 and around 24 hours from admission) and before implementation of COVID-19 therapy (except for oxygen support), as

were the levels of the basic inflammatory markers C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT). The thyroid levels were measured within 24 hours from admission to the hospital for COVID-19, regardless of the time of day. All patients included in the analysis received lab testing for thyroid hormones. No data was collected regarding the durations of symptoms.

Serum TSH, fT3 and fT4 were measured in a local laboratory (ECLIA - electrochemiluminescent method). The reference ranges were 0.27-4.2µU/ml (TSH) 3.1-6.8pmol/l (fT3) and 12.0-22.00 pmol/l (fT4). CRP, IL-6 and PCT were measured in a local laboratory (CRP - immunoturbidimetric method; IL-6 and PCT - ECLIA). High-Resolution Chest CT scans performed between 0 and 48 hours from admission were also examined to determine the percentage of lung parenchyma affected by COVID-19 lesions. For more detailed survival analyses, each group (ESS and non ESS) was classified into two subgroups with regard to the percentage lung involvement by COVID-19 lesions determined by visual quantification of CT images: 50% or less involvement, and more than 50% involvement. This is known a risk factor of early death or ICU admission, especially when lung involvement by pneumonia is more than 50% [15].

Clinical measures also included the use of supplemental oxygen therapy devices during hospitalization: HFNOT and invasive ventilation; length of hospitalization in days; need for remdesivir or tocilizumab therapy and mortality. Mortality was defined as death of patients in the hospital (non-ICU department or ICU department) and was evaluated by following up patients who continued treatment in ICU. The patients discharged from hospital were censored observations and not included in the outcome.

Statistical Analysis

Continuous variables not following a normal distribution were expressed as median with inter quartile range (IQR) and analyzed using the Mann-Whitney U-test. Categorical data were described using frequencies and percentages. The relationship between categorical variables was assessed with the chi square test (χ^2). The association between ESS and endpoints was determined using a Kaplan-Meier (KM) curve with a 95% confidence interval (95% CI).

A logistic regression model was created to evaluate the following potential risk factors to predict risk of mortality, HFNOT or intubation in cases of severe COVID-19: presence of ESS, percentage lung involvement of lesions (by chest CT), age, sex, smoking and pre-existing medical conditions: malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke or transient ischemic attack. Receiver operating characteristics (ROC) and area under the curve (AUC) analysis of mortality were used to evaluate the predictive power of the final model in predicting the need for intubation and HFNOT in response to risk factors for severe COVID-19. The goodness of fit of the model was tested with the Hosmer-Lemeshow statistic, where a nonsignificant probability value indicates a good fit. p-values lower than 0.05 were considered statistically significant.

Statistical analyses were performed using Statistica version 13 (StatSoft) and with GraphPad Prism version 7.0 software (GraphPad Software Inc., United States). Odds ratios were calculated with the use of a free online calculator: https://www.gigacalculator.com/calculators/odds-ratio-calculator.php.

Results

Baseline characteristics of patients with COVID-19

Among the 215 enrolled patients, 122 (56.7%) were male and 93 (43.3%) were female. The median age was 68 (IQR: 58–78) years old. ESS was diagnosed in 82 (38.1%) patients: 44 (53.7%) men and 38 (46.3%) women. The patients with ESS were older than the non-ESS patients: 73 years (IQR: 66.0; 82.3) vs 65 years (IQR: 52.5; 74.0) ($P < 0.001$). No sex dominance was observed between ESS and non-ESS groups ($P>0.05$). We carried out the analysis of outcomes to evaluate their relation with age and sex. Results are available in supplementary materials 1. Remdesivir was used in 47 (21.7%) cases and tocilizumab in 19 (8.8%) (Table 1). Angio-pulmonary CT scan was performed in 34 (15.8%) patients and pulmonary embolism was confirmed in 10 (4.7%). The risk factors for severe COVID-19 demonstrated in the patients are presented in Table 1. The most significent are: hypertension was present in 139 patients (64.7%), diabetes 60 patients (27.9%), coronary artery disease 45 (20.9%) heart failure in 23 patients (10.7%), history of stroke or transient ischemic attack 14 patients (6.5%), history of or current malignancy in 17 patients (7.9%), and pulmonary diseases (asthma, chronic obstructive pulmonary disease (COPD), overlap asthma-COPD syndrome) in 25 patients (11.6 %).

For further analyses, the COVID-19 patients were divided into Group 1 comprising those with ESS (n=82), and Group 2 without ESS (n=133).

For more detailed survival analyses, each group was classified into two subgroups with regard to the percentage of lung involvement by COVID-19 lesions: 50% or less involvement, and more than 50% involvement.

Data regarding the fT3, fT4, TSH levels and treatment of the studied groups are given in Table 1.

Laboratory findings on admission

The laboratory results of all included COVID-19 patients, with or without ESS on admission, are presented in Table 2. The results indicate that those with ESS had higher levels of inflammatory markers, including (CRP and PCT). Slightly higher IL-6 levels were observed among the patients with ESS; however, this difference was not significant ($p = 0.08$).

ESS is associated with a higher need for high flow nasal oxygen therapy and invasive ventilation in COVID-19 patients

The number of patients requiring HFNOT was 7/82 for ESS (8.5%) vs. 3/133 (2.3%) for non-ESS ($p<0.05$). The number of patients who were intubated and transferred to ICU 15/82 for ESS (18.3%) vs. 8/133 (6.0%) for non-ESS ($p<0.01$). Odds ratio with 95% CI and p-values for HFNOT and intubation for non-ESS patients and patients with ESS are given in Figure 1.

A logistic regression model was generated to evaluate the potential risk factors for severe COVID-19, i.e. ESS, percentage lung involvement identified on chest CT, older age, sex, smoking and pre-existing medical conditions (malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke or transient ischemic attack) to predict the risk of HFNOT or intubation. The final model is presented in Table 3. The presence of ESS and more than 50% involvement by COVID-19 lesions predispose the patient to increased chance of intubation. However, only more than 50% involvement by COVID-19 lesions was associated with a higher need for oxygen therapy in COVID-19 patients.

The Hosmer-Lemeshow test for goodness of fit indicated good calibration for the model (respectively for HFNOT $p = 0.999$, intubation $p = 0.743$). A ROC analysis for the

model (Figure 4) yielded an area under curve of 0.954 and 0.914 (95% CI: 0.916-0.992; 0.856-0.973 respectively for HFNOT and intubation).

ESS is associated with a higher risk of mortality in patients with COVID-19

Of the 215 patients, 41 (19.1%) died. Patients with ESS had a significantly higher mortality rate during hospitalization than those without ESS: 28/82 (34.1%) for those with ESS vs. 15/133 (11.3%) for those without ($p<0.0001$). The OR with 95% CI and p-values regarding mortality for both groups are given in Figure 1. Kaplan-Meier survival curves are shown in Figure 2B. Additionally, patients with ESS were more likely to stay in hospital than those without: The median time of hospital treatment was 10.5 days 95%CI (7;12) for ESS vs 9.5 days for non-ESS ($p<0.05$; Figure 2A).

A logistic regression model was generated to identify the selected severe COVID-19 risk factors to predict the risk of mortality. The final model is presented in Table 3. ESS, percentage lung involvement identified on chest CT and diabetes mellitus increase mortality in COVID-19 patients. The Hosmer-Lemeshow test for goodness of fit indicated good calibration for the model ($p = 0.793$). A ROC analysis for the model (Figure 4) yielded an area under curve of 0.888 (95% CI: 0.837-0.938).

Radiological findings on admission

Each patient had a chest CT scan performed, where % of COVID-19 inflammatory changes was assessed. CT scans were done in the same roentgenological laboratory, processed by the same team of technician of radiology and interpreted by the same two radiologists with specialization. All doubts were discussed and resolved by the same team. Imaging examinations showed that most patients (197/215; 91.6%) had inflammatory lesions. Patients with ESS were more likely to develop characteristic lesions in lung parenchyma

associated with COVID-19 confirmed by chest CT scan: 78/82 (95.1%) vs. patients without ESS 119/133 (89.5%) ($p<0.05$; Figure 3A). Kaplan-Meier curves indicate a lower survival probability in COVID-19 patients with ESS when chest CT findings at admission were 50% or less; no significant differences in survival were observed between ESS and non-ESS groups regarding lung involvement > 50% ($p= 0.19333$) (Figure 3 B, C).

Discussion

There is an urgent need to identify COVID-19 patients at a higher risk of a serious course of disease. Currently, the risk factors for COVID-19 include older age, male sex, and pre-existing medical conditions [16-18]. The European Centre for Disease Prevention and Control outlines health conditions reported among adult patients with severe COVID-19 disease: diabetes [18-20], obesity [21], hypertension [18,22,24], history of heart failure [22], solid organ tumors [23], ischemic heart disease [17,24,26], chronic respiratory disease [18,25], cancer [25, 27], pregnancy [28,31], neurologic conditions [22,25,26,29], COPD [22, 24], smoking [22,24,30] and chronic kidney disease [24-26].

However, while researchers have reported an association between thyroid dysfunction (TD) and COVID-19 severity [14, 32], as well as increased mortality among patients with TD and COVID-19 [33], ESS was not mentioned in the last data update from the European Center for Disease Prevention and Control (26 April 2021) [16] as a factor aggravating the course of COVID-19. To confirm whether ESS can be used to predict the severity of COVID-19, the present retrospective study was performed. Out of a group 310 patients hospitalized due to COVID-19 and approached to join the study, 215 met the inclusion criteria. The patients were divided into two groups based on fT3 level: an ESS group, defined as decreased fT3 levels (n=82), and a non-ESS group, defined as normal fT3 levels (n=133). The fact that that group of patients with ESS was relatively large is an additional strength of our work, as most

previous reports have based their findings on smaller numbers of patients with ESS (n=41) [14], (n=27) [6], (n=12) [33] or TD n=32 [32], n=25 [33], subnormal TSH (n=11) or low fT3 (n=12) [34].

Frequency of ESS in the group of patients diagnosed with COVID 19 admitted to our department was 38%. Frequency of ESS in patients diagnosed with COVID 19 in the literature ossilate between 6 % [32] and 27.52% [14]. Differences in prevelance of ESS may be explain by distinctions between examined populations for example median age of our cohort was 68 years vs median age of cohort from published articles was from 47 years [14] to 54 years [6][33]. Moreover prevelance of comorbidieties differentiate disussed populations. To clarify: our cohort hypertension, diabetes, cardiovascular disease had 64,7%, 27,9%, 20,9% of patients respectively while in population analyzed by Zhang at all [33] hypertension, diabetes, cardiovascular disease had 28,2%, 18,3%, 12,7% of patients respectively or by Zou et all [14] hypertension, diabetes, cardiovascular disease had 11,41%, 6,71%, 4,7% of patients respectively.

The two groups were compared with regard to selected parameters associated with COVID-19 course, , use of HFNOT or intubation, ICU hospitalization and death. For more detailed survival analysis, each group was subdivided according to the percentage of lung involvement by COVID-19 lesions: 50% or less, and more than 50%.

Visual quantification of CT lung lesions is a known risk factor of early death or ICU admission, especially when lung involvement is more than 50% [15]. The present study is the first to compare patients with ESS and those without ESS with regard to lung involvement with lesions according to CT imaging. While changes in the levels of most thyroid hormones can be used to predict the outcome of critically-ill patients, fT3 has the greatest power to predict ICU mortality [8]. Lower fT3 level has been found to be associated with greater mortality among ICU patients with ARDS [7]. Furthermore, thyroid hormones are known to

influence muscle strength [11], and reversible respiratory muscle weakness with diaphragmatic dysfunction has been identified in the course of hypothyroidism [9].

However, the prevalence of ESS and its association with the prognosis of COVID-19 remains unclear. Previous studies have reported that TD is closely associated with a higher mortality rate in patients with COVID-19. Zhang et al [33] report that patients with TD had a significantly higher mortality rate than those without TD during hospitalization (20% vs 0%; P = 0.002). Similarly, Lang et al [35] found a low fT3 state to be associated with an increased risk of in-hospital death after adjusting for confounding factors (HR 13.288, 95% CI: 1.089-162.110, P<0.05).

Our present findings indicate that patients with ESS demonstrated a significantly higher mortality rate, i.e. 28/82 (34.1%), than those without ESS, i.e. 15/133 (11.3%), during hospitalization (p<0.0001). Similarly, Schwarz et al. [5] report a mortality rate of 40% among COVID-19 patients with ESS . In addition, a low fT3 level may be a potential prognostic predictor of all-cause mortality in severe cases of COVID 19 [36]. A generated logistic regression model revealed that ESS is powerful predictor of COVID 19 mortality in hospitalized patients. The cost efficancy of recommeding to check thyroid panel to predict COVID 19 severity need to be calculated.

Additionally, our data indicates that patients with ESS had a longer length of hospital stay than those without ESS. The median time of hospital treatment was 10.5 days 95%CI (7;12) for the ESS group vs 9.5 days for the non-ESS group (p<0.05). COVID-19 patients with TD have been found to be more likely to stay in hospital for more than 28 days than those without TD [33]; however, no such difference was found in a similar study [5,14].

Our findings are the first to demonstrate an association between ESS and mortality in patients with 50% or less lung involvement by COVID-19. Kaplan-Meier curves indicated a lower survival probability in COVID-19 patients with ESS when chest CT findings at

admission were 50% or less; no significant differences were observed at involvement > 50% (p= 0.19333). In addition, a significantly higher number of patients with ESS were intubated and transferred to ICU than non-ESS patients. This suggest that ESS is a potential prognostic predictor, regardless of lung involvement by COVID-19. Previous studies have also noted that ESS may be an independent predictor of clinical deterioration in mild- to moderate-severity COVID-19 patients [6].

This is the first study to investigate the relationship between higher need for high flow nasal oxygen therapy and invasive ventilationduring hospitalization and lung involvement, identified by chest CT (%), in COVID-19 patents with ESS or without ESS. The patients with ESS demonstrated a significantly higher risk of HFNOT andinvasive ventilation. Unexpectedly, we also observed a lower median % involvement of lung lesions on chest CT in the ESS group than in the non-ESS group when analysed with regard to need for (mechanical ventilation; this can be partially explained by the influence of thyroid hormones on muscle function [7]. While the effects were not statistically significant, there is clearly a noticeable tendency that requires research on a larger group of patients.

In addition, a logistic regression model was used to evaluate the predictive potential of selected risk factors for severe COVID-19 on the risk of mortality, HFNOT and intubation. The analysis confirmed our previously presented results. ESS and percentage lung parenchyma involvement by COVID-19, i.ecan predict increased risk of mortality and intubation in COVID-19 patients. The analysis also found diabetes to be a predisposing factor for increased mortality for both patients with ESS and without ESS: no significant differences in the incidence of diabetes were found between the two groups. In turn, only percentage lung involvement identified on chest CT is a factor predicting a higher need for oxygen therapy in COVID-19 patients. However, the Kaplan-Meier curve indicated that the patients with ESS had a lower probability for survival than those without ESS at < 50% percentage lung

involvement identified on chest CT; no differences in mortality were observed when comparing those with > 50% parenchymal involvement.

Our findings also indicate that COVID-19 patients with ESS tended to present with persistently higher inflammatory biomarkers (CRP and PCT). However, it should be noted that the level of PCT in both ESS and non-ESS patients was within normal ranges. This further indicates that ESS might be closely associated with a more severe inflammatory response. The results of our research on inflammatory biomarkers are consistent with previous reports conducted by Zhang et al [33] and Zou et al [14]. It has been shown that patients with severe COVID-19 infection may undergo a cytokine storm characterized by hyperactivity of the Th1/Th17 immune response, with increased production of several pro-inflammatory cytokines, including IL-6, interleukin 1 B (IL1B) and tumor necrosis factor alpha (TNF-α) [37]. In the present study, no significant difference in IL-6 level was found between patients with ESS and without ESS; however a slight increase was observed in patients with ESS: 36.4 (24.9; 94.5) with ESS vs 51 (19.8; 85.9) without ESS ($p = 0.08$). In summary, ESS is a common condition and this should be taken into account when performing thyroid function tests on COVID 19 patients. Knowledge about the pathophysiology and course of ESS should be established among clinicians involved in treatment of patients with SARS-CoV-2 infection. Thyroid hormones are known to influence muscle strength [8], and reversible respiratory muscle weakness with diaphragmatic dysfunction has been identified in the course of hypothyroidism [13, 14]. Exist a list of well known and established risk factors of a serious course of COVID-19 [16] neverthelessan awareness of the potential impact of ESS on the course of COVID-19 may help qualify patients to certain department upon hospitalization (e.g. departments with access to HFNOT).

Conclusions

ESS appears to be closely associated with poorer prognosis, including longer hospitalization, a higher frequency of intubation and transferal to ICU, and a higher mortality rate. The fact that the ESS group demonstrated higher mortality even when chest CT findings at admission were 50% or less suggests that ESS is potential prognostic predictor, regardless of lung involvement by COVID-19. Our results indicate that special attention and more intensive surveillance should be considered for COVID-19 patients with ESS.

Limitations

This study has several limitations. Firstly, the patients were transferred to the hospital at different times from the onset of illness. Secondly, it remains unclear whether the presence of ESS and age are independent risk factors of death in patients with COVID 19 or whether a correlation exists between the two variables.

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468 **List of figure captions**

469

470 **Figure 1.** Odds ratio (OR) for patients with ESS and non-ESS patients for death, intubation
471 and high flow nasal oxygen therapy (HFNOT).

472

473 **Figure 2AB. A:** Hospitalization time in patients with ESS vs. non-ESS patients: median 10.5
474 days interquartile range - IRQ (8; 13) for ESS vs. 9.0 days IRQ (7; 12) for non-ESS ($p<0.05$).
475 **B:** Kaplan-Meier curve for mortality in COVID-19 patients with ESS vs. non-ESS patients
476 ($p=0.00281$).

477

478 **Figure 3ABC. A:** Median lung inflammatory infiltration in COVID-19 patients: 30%
479 interquartile range - IRQ (15; 60%) for ESS vs 25% IRQ (10; 40) for non-ESS ($p<0.05$).
480 Kaplan-Meier curve for mortality in COVID-19 patients with ESS vs. non-ESS patients, **B**:
481 with lung involvement by COVID 19 changes 50% or less ($p=0.00417$), **C:** with lung
482 involvement by COVID 19 changes more than 50% ($p= 0.19333$); CT - computed
483 tomography.

484

485 **Figure 4 ABC.** ROC curve analysis for the **A:** mortality, **B:** intubation, **C:** HFNOT model in
486 predicting response to the risk factors for severe COVID-19 include ESS, percentage lung
487 involvement identified on chest CT, older age, sex, smoking and pre-existing medical in
488 patients with COVID.

489

Table 1. Characteristics of the COVID-19 patients with ESS and those without.

Parameter Median/ (IQR)	**Total patients N=215**	**Patients with ESS n=82**	**Non-ESS patients n=133**	**P**
Sex				
n, % female	93 (43.3)	38 (46.3)	55 (41.4)	P>0.05
n, % male	122 (56.7)	44 (53.7)	78 (58.4)	
Age (years)	68 (58; 78)	73 (66.0; 82.3)	65 (52.5; 74.0)	**p<0.001**
TSH (µU/ml; normal range 0.27- 4.2)	1.1 (0.6; 1.6)	1.07 (0.6; 1.7)	1.10 (0.6; 1.7)	P>0.05
FT3 (pmol/l; normal range 3.1-6.8)	3.3 (2.6; 4.0)	2.5 (2.2; 2.8)	3.7 (3.4; 4.3)	**P<0.0001**
FT4 (pmol/l; normal range 12.0-22.00	17.1 (14.5; 19.7)	16.4 (13.3; 19.3)	17.8 (15.0; 20.3)	**P<0.05**
Medication, n (%)				
Remdesivir	47 (21.7)	15 (18.3)	32 (24.1)	p>0.05
tocilizumab	19 (8.8)	9 (11.0)	10 (7.5)	p>0.05
Pre-existing medical conditions and risk factors for severe COVID-19				
Malignancy	17 (7,9)	6 (7,3)	11 (8,3)	P>0.05
Hypertension	139 (64,7)	55 (67,1)	84 (63,1)	P>0.05
Diabetes Mellitus	60 (27,9)	25 (30,5)	35 (26,3)	P>0.05
Chronic lung disease	25 (11,6)	12 (14,6)	13 (9,8)	P>0.05
Chronic kidney disease	20 (9,3)	8 (9,7)	12 (9,0)	P>0.05

Chronic Liver Disease	25 (11,6)	7 (8,5)	18 (13,5)	P>0.05
Heart failure	33 (15,3)	16 (19,5)	17 (12,8)	P>0.05
Coronary Artery Disease	45 (20,9)	22 (26,8)	23 (17,3)	P>0.05
Stroke or transient ischemic attack	14 (6,5)	8 (9,7)	6 (4,5)	P>0.05
Smoking	27 (12,5)	9 (10,9)	18 (13,5)	P>0.05
Obesity	49 (22,8)	12 (14,6)	37 (27,8)	**P<0.05**

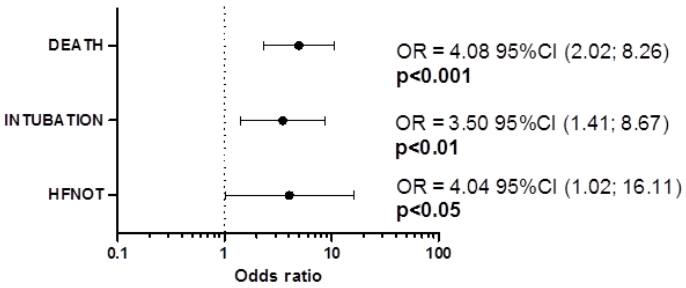
Table 2. Laboratory findings of COVID-19 patients at admission.

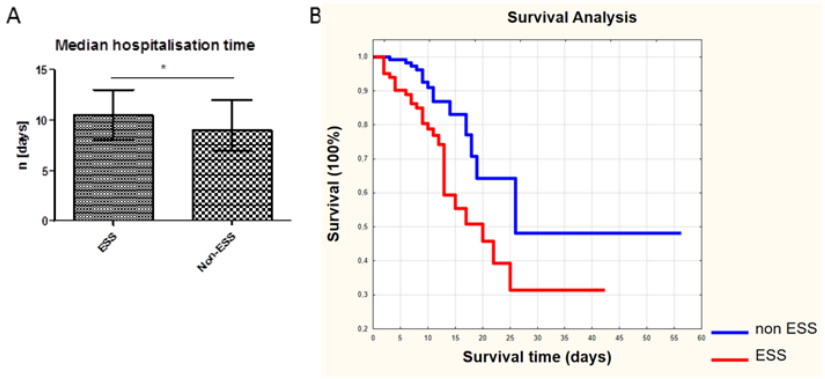
Parameter Mediana/(IQR)	**Total patients** **N=215**	**Patients with ESS** **n=82**	**Non-ESS patients** **n=133**	**P**
CRP (mg/l ; normal range < 5.0)	71.4 (26.8; 124.1)	79.3 (39.1; 142.5)	61.5 (22.0; 111.8)	**P<0.05**
PCT (ng/l ; normal range < 0.5)	0.12 (0.1; 0.3)	0.15 (0.07; 0.2)	0.11 (0.1; 0.6)	**P<0.0001**
IL-6 (ng/ml; normal range < 7.0)	43.10 (21.1; 87.3)	51.0 (19.8; 85.9)	36.4 (24.9; 94.5)	P>0.05

Table 3. Multivariate regression model for predicting mortality, intubation and HFNOT in response to selected risk factors for severe COVID-19 (include ESS, percentage lung involvement identified on chest CT (0-100%; 0-50% and more than 50%), older age, sex, smoking and pre-existing medical: malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke or transient ischemic attack) in patients with COVID-19. Only statistically significant data is included in the table.

Mortality			
	OR	95% CI	p value
ESS	3,163	1,276 to 8,225	**P<0.05**
ESS when 50% or less lung involvement identified on chest CT	3,870	1,091 to 11,19	**P<0.05**
Percentage lung involvement identified on chest CT (0-100%)	1,052	1,033 to 1,074	**P<0.0001**
Diabetes Mellitus	3,35	1,325 to 8,859	**P<0.05**
Intubation			
ESS	4,155	1,145 to 17,54	**P<0.05**
ESS when 50% or less lung involvement identified on chest CT	4,421	1,158 to 18,23	**P<0.05**
Percentage lung involvement identified on chest CT (0-100%)	4,256	0,9178 to 0,9678	**P <0.0001**
HFNOT			

Percentage lung involvement identified on chest CT (0-100%)	1,099	1,408 to 1,480	**P<0.001**





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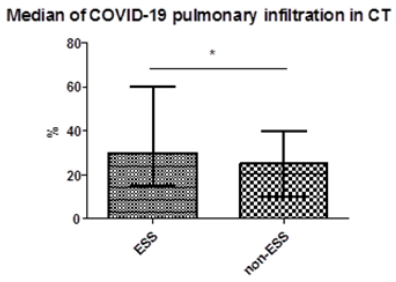

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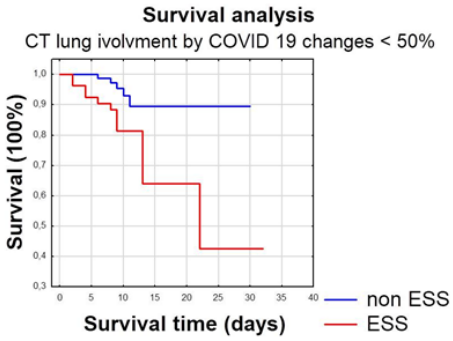

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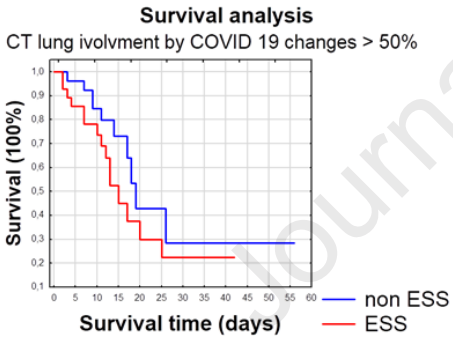

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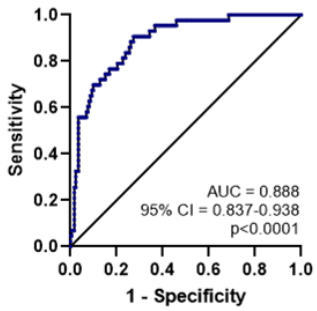

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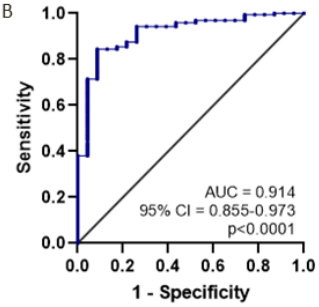

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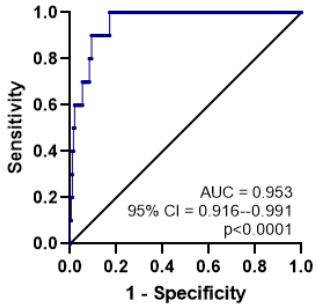
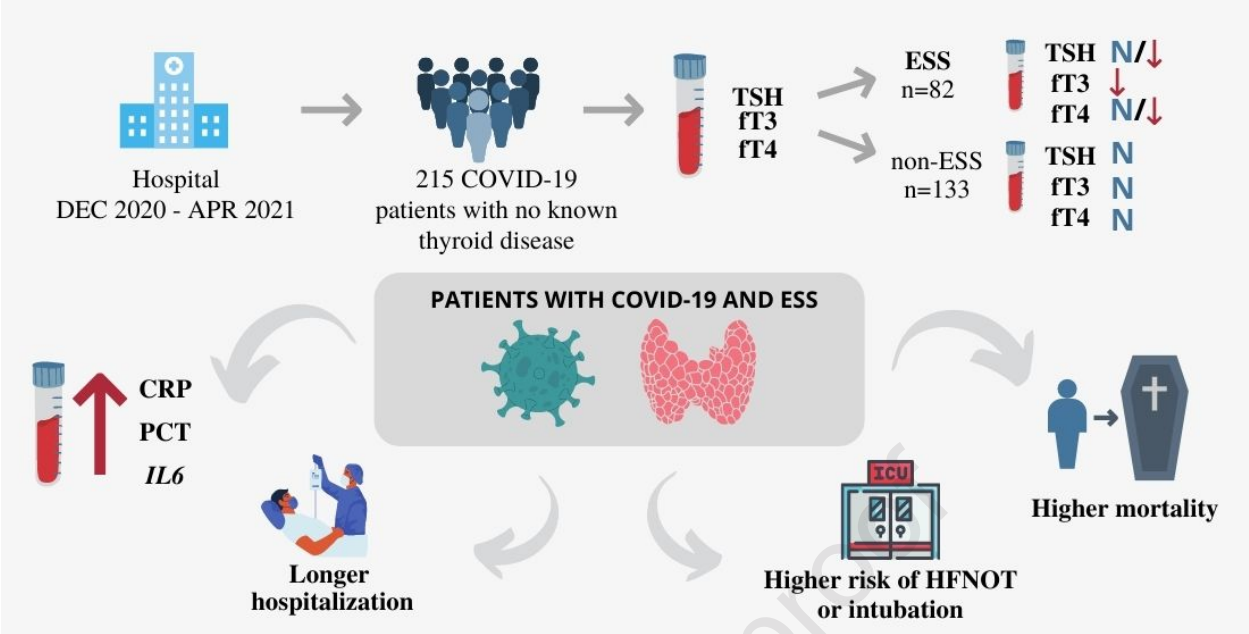
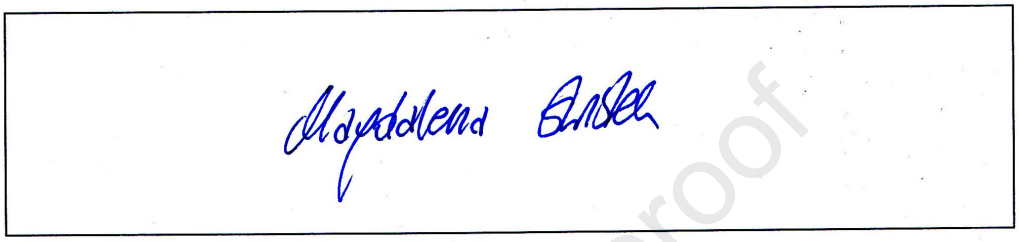




Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



ESS appears to be closely associated with poorer prognosis and a higher mortality rate.

ESS group demonstrated higher mortality even when chest CT findings at admission were 50% or less.

ESS is potential prognostic predictor, regardless of lung involvement by COVID-19.

Clinical Relevance

Special attention and more intensive surveillance should be considered for COVID-19 patients with ESS. An awareness of the potential impact of ESS on the course of COVID-19 may help qualify patients to certain department upon hospitalization. ESS is potencial prognostic predictor regardless of lung involvment by COVID-19.